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DOI:
10.1210/jc.2017-02025

Document Version
Peer reviewed version

Citation for published version (Harvard):
Uday, S, Gaston, L, Rogers, L, Parry, M, Joffe, J, Pearson, J, Grimer, R & Högler, W 2018, 'Osteonecrosis of the jaw and rebound hypercalcaemia in young people treated with denosumab for giant cell tumour of bone', *Journal of Clinical Endocrinology and Metabolism*, vol. 103, no. 2, pp. 596–603. https://doi.org/10.1210/jc.2017-02025

Osteonecrosis of the jaw and rebound hypercalcaemia in young people treated with denosumab for giant cell tumour of bone

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Short title: Denosumab related adverse effects in adolescents

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Word Count: **Abstract: 245** **Manuscript: 2755**

Figures: 2 **Tables: 2**

Precise: We highlight the serious adverse effects of fixed high-dose denosumab in adolescents including osteonecrosis of the jaw on treatment and rebound hypercalcaemia following treatment cessation.

Key Words: Antiresorptive therapy, bisphosphonates, bone remodelling, rebound hypercalcemia, hypocalcaemia, denosumab

Abstract:

Context: Denosumab, an inhibitor of receptor activator of nuclear factor kappa-B ligand, is an approved treatment for giant cell tumour of bone (GCTB) in adults and 'skeletally mature' adolescents. Safety concerns include oversuppression of bone remodelling, with risk of osteonecrosis of the jaw [ONJ] and atypical femur fractures during treatment in adults, and rebound hypercalcaemia after treatment cessation in children. To date, ONJ has never been reported in children or adolescents.

Objectives: To describe serious adverse effects during and following high-dose denosumab therapy in GCTB patients.

Patients: Two adolescents (14 and 15 years) and a young adult (40 years) received fixed denosumab for GCTB for 1.3 - 4years (cumulative dose 47-98 mg/kg), which was stopped due to development of ONJ in one adolescent and bilateral femoral cortical stress reactions in the young adult. All three patients developed rebound hypercalcaemia with acute kidney injury 5.5 - 7 months after denosumab cessation.

Results: The ONJ necessitated surgical debridement. Rebound hypercalcaemia (serum calcium 3.1-4.3mmol/L) was unresponsive to hyperhydration alone, requiring repeated doses of calcitonin or intravenous bisphosphonate treatment. Hypercalcaemia recurred in 2 patients within 4 weeks, with normal serum calcium profiles thereafter. All patients were naïve to chemotherapy, radiotherapy, bisphosphonates, corticosteroids and metastases free, confirming the causative role of denosumab in these complications.

Conclusion: These suppression-release effects of high-dose denosumab on bone remodelling raise questions about safety of fixed dosing and treatment duration. In young people weight-adjusted dosing and safety monitoring during and after antiresorptive therapy is required.

Introduction

Giant cell tumour of bone (GCTB) is a benign, locally aggressive tumour with malignant potential (1) affecting young adults, usually in the 3rd and 4th decade of life. The majority of patients are effectively treated with intralesional curettage whilst some patients with extensive, aggressive, and/or incompletely resectable tumours require excision and reconstruction or even joint sacrificing surgery given the predilection of the tumour for apophyseal locations (1).

GCTB is characterised by the presence of multi-nucleated, osteoclast-like giant cells (2). The neoplastic stromal cells express high concentrations of receptor activator of nuclear factor kappa-B ligand (RANKL) which activates its receptor RANK on giant cells and their precursors (2). Denosumab is a human monoclonal antibody that neutralizes the activity of RANKL and therefore suppresses osteolytic bone destruction in GCTB (3). Greater than 90% elimination of giant cells after 25 week treatment with high-dose denosumab (120 mg subcutaneously on day 1, 8, 15, 28 and then every 4 weeks thereafter) has been reported (n=20) (4). Denosumab is approved by Food and Drug Administration and European Medicines Agency for the treatment of GCTB, in adults and skeletally mature adolescents, when the tumour is deemed unresectable, requires morbid surgery, or in metastatic disease. However, uncertainties regarding treatment duration remain (5).

The main safety concern of antiresorptive therapy relates to the oversuppression of bone remodelling. In adults, bisphosphonates have been implicated in the development of osteonecrosis of the jaw (ONJ) (6) and atypical femoral fractures (7) which has led to restrictions in treatment duration. High-dose denosumab therapy also causes ONJ and atypical femoral fractures in 6% and 4%, respectively of adults treated for GCTB (5). Due to the potent and rapid on-off effects on osteoclastic bone resorption, rebound hypercalcaemia

following treatment discontinuation has emerged as a relatively new adverse event specific to denosumab (8).

In children and adolescents with osteogenesis imperfecta and osteoporosis, prolonged or high dose bisphosphonate therapy has been associated with iatrogenic osteopetrosis (9) and suspected atypical femoral fractures (10,11), but never with ONJ (12) or rebound hypercalcaemia. To date, safety data for denosumab in adolescents are sparse since only 3.5% (n=10 of 282) of patients in the GCTB safety trial were adolescents (aged 13-17 years) (3). Low-dose denosumab therapy (1 mg/kg 12 weekly over 48 weeks) was found to be safe in a small number (n=10) of paediatric patients with osteogenesis imperfecta (13). However, four cases of rebound hypercalcaemia following cessation of denosumab (doses ranging from 0.5 mg/kg to 120 mg in GCTB) have been reported in children (aged 8-10 years), and attributed to their physiologically higher bone turnover (14-17). The safety of prolonged use of denosumab in adolescents remains unknown due to a dearth of long term follow up studies.

Here we report rebound hypercalcaemia with acute kidney injury following denosumab cessation in three young people with GCTB. Denosumab therapy had been stopped in two of them because of the development of ONJ in the adolescent and bilateral femoral cortical stress reactions in the young adult.

Case Descriptions

Individuals described here had a confirmed histological diagnosis of GCTB and received denosumab, 120mg subcutaneously on day 1, 8, 15, 28 and then every 4 weeks as part of a phase three clinical trial (ClinicalTrials.gov Identifier: NCT00680992) (18). All patients received fixed doses irrespective of age or weight as per the protocol but for different durations. Patient demographics, disease specifications, treatment indications, dose and

duration and reason for treatment cessation are detailed in **Table 1**. **Table 2** details the biochemical picture at presentation of rebound hypercalcaemia and its management.

Patient 1

Diagnosis and initial management:

A 15-year old male with biopsy-proven GCTB of the sacrum received denosumab for unresectable, recurring tumour despite previous embolisation and curettage. 'Skeletal maturity' was confirmed as per trial protocol (defined as radiographic evidence of at least one mature long bone [with closed epiphyseal growth plate] in ≥ 12 year old adolescents). Ongoing clinical and radiological response was seen from 3 months.

Osteonecrosis of the jaw (ONJ):

In the fourth year of denosumab treatment (after 44 doses), the patient (then aged 19 years) underwent dental extraction for a chipped tooth sustained whilst playing football. The risk of developing ONJ was discussed and the patient advised on dental hygiene and smoking cessation. Weighing up the risks of developing ONJ against recurrence of GCTB, denosumab was continued after ensuring complete healing of mucosa in the extraction socket with no exposed bone. Two months later he presented with acute pain at the dental extraction site. ONJ stage two was diagnosed (**Figure 1A**) as per the classification adopted by American Association of Oral & Maxillofacial Surgeons (6). Denosumab was stopped after a total of 46 doses (cumulative dose of 98mg/kg). Swab of the affected area showed heavy growth of streptococci milleri and a moderate growth of alpha-haemolytic streptococcus. The ONJ was initially managed conservatively (amoxicillin, metronidazole and mouthwash) with poor healing, necessitating debridement and sequestrectomy of the exposed bone. A moderate amount of necrotic bone around the extraction socket of the left mandible was debrided with

subsequent full recovery. Clear demarcation between necrotic and normal bone was noted at surgery.

Rebound hypercalcaemia with acute kidney injury:

Seven months after stopping denosumab the patient presented with a 3-week history of nausea, vomiting and generalised body pain. Investigations identified raised serum calcium (3.1 mmol/L) **(Figure 2A)** and creatinine indicating acute kidney injury. Serum phosphate and alkaline phosphatase were normal, 25-hydroxy vitamin D was low and parathyroid hormone appropriately suppressed **(Table 2)**, with normal thyroid function. An MRI scan and bone scintigraphy demonstrated no evidence of local or metastatic disease. C-terminal telopeptide of type I collagen was elevated (3.07 microg/L [normal range 0.016-0.584]) confirming increased bone resorption and the diagnosis of rebound hypercalcaemia secondary to denosumab discontinuation was made.

Management and progress:

Hypercalcaemia persisted despite hyperhydration (volume expansion) and resolution of the acute kidney injury. Since bisphosphonates were considered contra-indicated due to ONJ and renal failure, calcitonin **(Table 2)** was administered on day 0 (D0). Normocalcaemia was only achieved following a second dose on D2 **(Figure 2A)**.

Despite compliance with high volume oral hydration at home, symptomatic hypercalcaemia recurred on D19 and D33 requiring readmission for hyperhydration and calcitonin **(Figure 2A).** On each re-challenge with calcitonin, control of hypercalcaemia was more durable. Eighteen months after stopping denosumab, he remained normocalcaemic on a high volume oral fluid regimen, ONJ had healed and there was no tumour recurrence.

Patient 2

Diagnosis and initial management:

A 14-year old female with sacral GCTB received neoadjuvant treatment with denosumab due to the extent of the tumour. MRI scans showed a reduction in tumour volume after 12 doses and she underwent a partial sacrectomy; histology confirmed 50% loss of giant cells in keeping with a response to denosumab. A further 6 doses of denosumab every 4 weeks post-operatively were administered, with a cumulative dose of 47 mg/kg. A full recovery was made with resolution of the lower back pain noted on presentation and return to full weight bearing activities.

Rebound hypercalcaemia with acute kidney injury:

Six months after the last dose of denosumab, the patient (aged 15.9 years) experienced increasing back pain, paraesthesia of her legs and nausea. An MRI scan showed no evidence of recurrence or metastases. Investigations revealed marked hypercalcaemia (serum calcium 3.4 mmol/L) **(Figure 2B)** with acute kidney injury. Denosumab-induced rebound hypercalcaemia was diagnosed following exclusion of other causes, i.e hyperparathyroidism and thyrotoxicosis **(Table 2)**. 25 hydroxy vitamin D levels were very low.

Management and progress:

Hyperhydration (150% maintenance) was commenced and single dose of frusemide (1 mg/kg) was administered on D0 to induce calciuresis. Since continued hyperhydration over 5 days was unsuccessful in resolving hypercalcaemia, low dose pamidronate **(Table 2)** was administered on D5 and D6 (**Figure 2B)**. Calcium normalised on D7 and previously suppressed parathyroid hormone improved to 29 ng/L. A single dose of cholecalciferol (150,000 IU) followed by daily vitamin D (400 IU) and calcium supplements (1.2 g three times a day) were commenced. Symptomatic hypocalcaemia nevertheless occurred, requiring one bolus dose of IV calcium, followed by oral calcium supplementation which was weaned

over 4 weeks. Severe bone pain, initially managed with ibuprofen and morphine, responded very well to pamidronate. Serum calcium remains stable one year after pamidronate with no further episodes of rebound hypercalcaemia. GCTB remains under remission.

Patient 3

Diagnosis and initial management:

A 40-year old male, with very large and vascular GCTB of the scapula opted for denosumab treatment. Clinical and radiologic response to treatment was achieved and denosumab continued to avoid morbid surgical resection of the whole scapula. After 51 doses of denosumab therapy (cumulative dose of 51 mg/kg) the patient presented with bilateral thigh pain. Plain radiographs did not reveal any identifiable lesions; therefore a single photon emission computed tomography scan was undertaken which revealed increased tracer uptake on the medial cortex of both proximal femora, the area of clinical concern **(Figure 1B)**. Since such femoral cortical stress reactions are association with antiresorptive agents (7), denosumab therapy was stopped. Thigh pain settled with denosumab cessation and did not necessitate any treatment.

Rebound hypercalcaemia and acute kidney injury:

The patient presented to the emergency department 5.5 months after denosumab cessation with drowsiness, polyuria, polydipsia and vomiting. On presentation, hypercalcaemia (serum calcium 4.27 mmol/L) and acute kidney injury **(Table 2)** was diagnosed, which was managed with hyperhydration and ibandronate **(Figure 2C).** Parathyroid hormone was appropriately suppressed. The patient presented again on D33 with a further episode of hypercalcaemia, which was managed with hyperhydration alone. At restaging, 7.5 months from stopping

denosumab, a relatively small focal recurrence was identified relative to the overall dimensions of the initial tumour on MRI and was confirmed on biopsy. This has been managed by subtotal scapulectomy.

Discussion

Prolonged, potent antiresorptive therapy (including bisphosphonates and denosumab) in adults is associated with ONJ and atypical femoral fractures. To date, these serious adverse effects have not been reported in children and adolescents. Here we report the first case of ONJ in an adolescent (P1) and femoral cortical stress reactions in a young adult (P3) receiving treatment with fixed high-dose denosumab for GCTB. The fact that these two patients and another adolescent also developed rebound hypercalcaemia and acute kidney injury following treatment cessation raises serious safety questions. All patients were naïve to chemotherapy, radiotherapy, bisphosphonates and had no evidence of metastatic disease, confirming the causative role of denosumab in these complications.

Antiresorptive therapy in children is generally considered safe. However, the case of a child who developed iatrogenic osteopetrosis with tube-like, dense metaphyses during prolonged, high-dose bisphosphonate therapy has raised safety concerns amongst paediatric bone specialists (9). Side-effects of standard-dose bisphosphonate therapy include typical metaphyseal sclerotic bands which are also seen in denosumab treatment (19). Bisphosphonates have also been associated with suspected atypical femoral fractures in children (10,11) although not confirmed in larger series (20,21). Several studies have assessed the risk of developing ONJ in bisphosphonate-treated children following dental treatment (22, 23), however no cases have been reported so far.

Medication or antiresorptive agent-related ONJ (6) has been associated with risk factors such as smoking, old age, poor oral hygiene, invasive dental procedures, serious comorbidities and concomitant treatments (18). ONJ has been reported in nearly six per cent of GCTB treated patients (5). Patient 1 developed ONJ following a dental extraction, a known major risk factor reported by 52-61% of adult ONJ patients, with greatest risk in those on intravenous bisphosphonates (6). He was also a smoker and had poor dental hygiene, hence had several risk factors for developing ONJ.

The risk of ONJ in adults on antiresorptive treatment is dose and duration dependent (5). The fixed denosumab dose of 120mg 4 weekly is based on 90% suppression of urinary N-telopeptide normalised to urinary creatinine (uNTx/Cr) in adults (n=373) with bone metastases from solid tumours (24). Whilst to date no study has determined appropriate paediatric doses, these high doses were anticipated to be safe in adolescents weighing over 45kg with closed growth plates, extrapolated from data in adults with GCTB weighing as low as 38kg (18). However, bone metabolism in young people differs from adults, and includes bone modelling and elongation, with bone accrual into their late twenties, long after closure of growth plates (25). The teenage GCTB patients reported here, and those in other reports (14,15), indicate an urgent need to consider weight-based dosing and systematic safety studies. Although the rate and extent of uNTx/Cr suppression are reported to remain constant at denosumab doses above 0.3 mg/kg, the duration of maximum suppression increases with increasing doses (26,27). Moreover, denosumab displays a dose-proportional increase in exposure at doses higher than 60mg. Of note, the incidence of denosumab related ONJ in prostate cancer patients is reportedly higher in clinical practice (28) when compared to trials (29) (11·4% vs 2·3% respectively). Hence, the clinical implications and safety of cumulative doses over a prolonged period of time require further studies (30).

Patient 3 developed femoral cortical stress reactions in the proximal femur bilaterally. Atypical femoral fractures have been linked to denosumab (5). The incidence of femoral cortical stress reactions in metastatic bone disease patients receiving denosumab is reported to be around 4·5% (31). Femoral cortical stress reaction is recognised as a prodrome of atypical femoral fracture (31-34). Unlike previous reports P3 did not have osteoporosis, metastatic disease and was not exposed to bisphosphonates or corticosteroids indicating the independent role of denosumab in the causation of femoral cortical stress reactions.

Hypocalcaemia during denosumab treatment is well recognised as a sign of rapid suppression of bone remodelling (3), however rebound hypercalcaemia due to rapid release of previously suppressed remodelling is less known, hence unmonitored. There are four reported cases of rebound hypercalcaemia following denosumab cessation in children, occurring between 7 weeks - 5 months after treatment cessation. Two juvenile patients with GCTB received high dose denosumab (14,15), the third, a 9 year old boy with fibrous dysplasia, received a starting denosumab dose of 1 mg/kg increasing up to 1.75 mg/kg with 0.25 mg/kg dose increments 3 monthly (16) and the fourth, an 8 year old girl with Paget's disease received 0.5 mg/kg (17).

Rebound hypercalcaemia is due to osteoclast overactivity after denosumab cessation and is thought to be a feature of skeletally immature children due to high bone turnover. Quite in contrast, P3, aged 40, and another reported adult, aged 60, also experienced rebound hypercalcaemia (8), indicating that this side effect is not restricted to young patients. Whilst hypercalcaemia can be a sign of tumour reactivation, there was no such evidence in our patients. Similar to previous reports (14,15) all our patients had parathyroid hormone-independent hypercalcaemia. Suppressed parathyroid hormone noted at presentation improved following treatment of hypercalcaemia (P2).

Currently, there are no data on the incidence of rebound hypercalcaemia, and no monitoring or management guidelines. The mean half-life of denosumab after cessation is reported to be 29 days (range 25-35 days) (27). However, the clearance is likely to be longer in individuals with accumulated doses, hence the occurrence of rebound hypercalcaemia as late as 7 months from treatment cessation. Possibly, the presence of vitamin D deficiency in P1 and P2 delayed their presentation. Hypercalcaemia responded poorly to hydration alone, so P1 was managed with calcitonin in the setting of ONJ and renal failure, and P2 and P3 with low dose pamidronate and ibandronate. A previous report described resistance to a combined use of calcitonin, pamidronate and corticosteroids, necessitating the use of low dose denosumab (15). Whilst the prolonged antiresorptive action of bisphosphonates is an effective treatment for hypercalcaemia in this setting, the presence of acute kidney injury increases the risk of bisphosphonate-induced renal failure. None of the patients reported here were monitored for rebound hypercalcaemia and presented unwell and in pain, requiring extensive investigations to rule out other causes of hypercalcaemia. The increasing use of denosumab necessitates monitoring and increased awareness amongst clinicians and patients.

Conclusions:

The effect that denosumab has on GCTB size reduction is remarkable, but the necessity for high-dose long-term antiresorptive therapy comes at the price of suppression of bone remodelling which in adults includes the risk of osteonecrosis of the jaw and atypical femoral fractures. Denosumab, with its potent suppression-release effects has introduced the additional complications of hypocalcaemia at drug commencement and rebound hypercalcemia after discontinuation. This first case of ONJ in an adolescent and the substantial morbidity from rebound hypercalcaemia after treatment discontinuation in our young patients stresses the need to consider weight-adjusted dosing, frequency and duration

of treatment, and develop tools to monitor treatment. A systematic monitoring of serum calcium and pain for a minimum of 7 months after treatment cessation should be adopted.

Conflict of interest:

None declared

Acknowledgements:

We are grateful to Zaira Akhtar, Birmingham Medical School and Claudette Jones, Royal Orthopaedic Hospital Research Nurse, for assisting in data collection.

Funding:

None

Consent:

Consent for publication has been obtained from all patients. Amgen have had the opportunity to comment on the manuscript.

Contributorship statement:

SU: Preparation of manuscript, data acquisition, data analysis, editing figures, final approval

LG: Data acquisition, data analysis, editing manuscript

LR: Data acquisition, creating graphs

MP: Intellectual revision of manuscript and final approval

JJ: Intellectual revision of manuscript

JP: provided images and revision of manuscript

DS: intellectual revision of manuscript

RG: concept and intellectual revision of manuscript

WH: Design, concept, manuscript preparation, intellectual revision of manuscript and final approval

Disclosures:

RG has previously consulted for Amgen

WH is a co-investigator in Amgen trial in osteogenesis imperfect

SU, LG, LR, MP, JJ, JP, DS have nothing to disclose

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Figure legends

Figure 1: Side effects during denosumab therapy:

Fig 1A: Osteonecrosis of the jaw (circled) in patient 1, demonstrating an area of non- healing, exposed bone in the mandible following the removal of a permanent lower left first molar tooth.

Fig 1B: Single photon emission computed tomography scan on patient 3 demonstrating increased tracer uptake representing bilateral femoral cortical stress reactions (arrows), and the giant cell tumour of the right scapula.

Figure 2: Rebound hypercalcaemia following denosumab discontinuation: Serum calcium levels (corrected for albumin, cCa^{2+}) at presentation and response to treatment in patient 1 (A), patient 2 (B) and patient 3 (C). Interventions are indicated with arrows and lower (LL) and upper (UL) normal ranges for serum calcium are indicated by horizontal lines.